

Electronic Supplementary Information for

Gadolinium Complexes of Monophosphinic Acid DOTA Derivative Conjugated to Cyclodextrin Scaffolds: Efficient MRI Contrast Agents for Higher Magnetic Fields

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Set of equations used for fitting of relaxometric data.

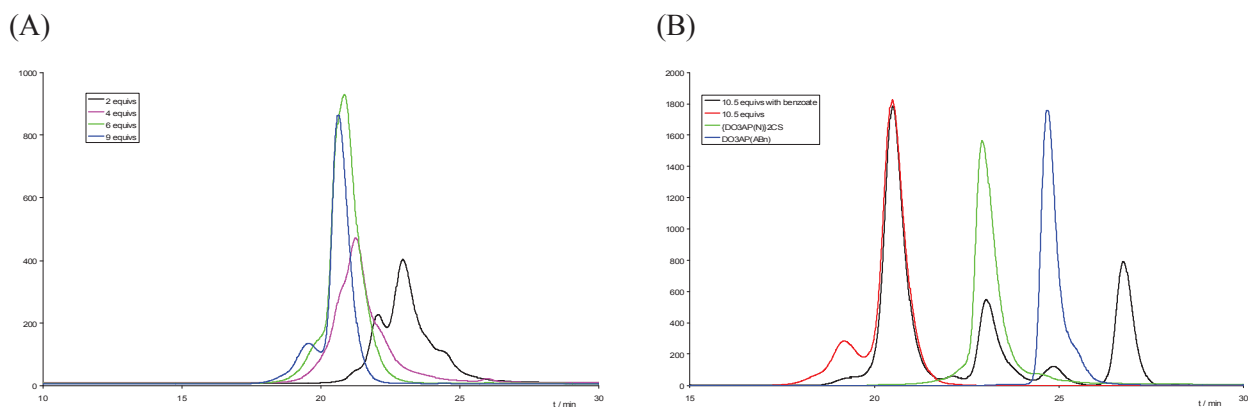


Fig. S1. (A) SE-HPLC chromatograms of products from reaction of α -CD-(NH₂)₆ with 2 (black), 4 (magenta), 6 (green) and 9 equivs of DO3AP^{NCS}; the reaction mixtures were worked-up by ultrafiltration using membrane with 1 kDa cut-off. (B) Comparison of SE-HPLC chromatograms of product from reaction between β -CD-(NH₂)₇ and 10.5 equivs of DO3AP^{NCS} (separated by ultrafiltration using 3 kDa membrane, red) and reaction mixture of β -CD-(NH₂)₇ with 10.5 equivs of DO3AP^{NCS} in presence of 20 equivs of benzoate (black). The chromatograms of DO3AP^{ABn} (blue) and the ditopic byproduct (DO3AP^N)₂CS (green) are shown for the comparison. The last peak (~27 min) corresponds to the benzoic acid.

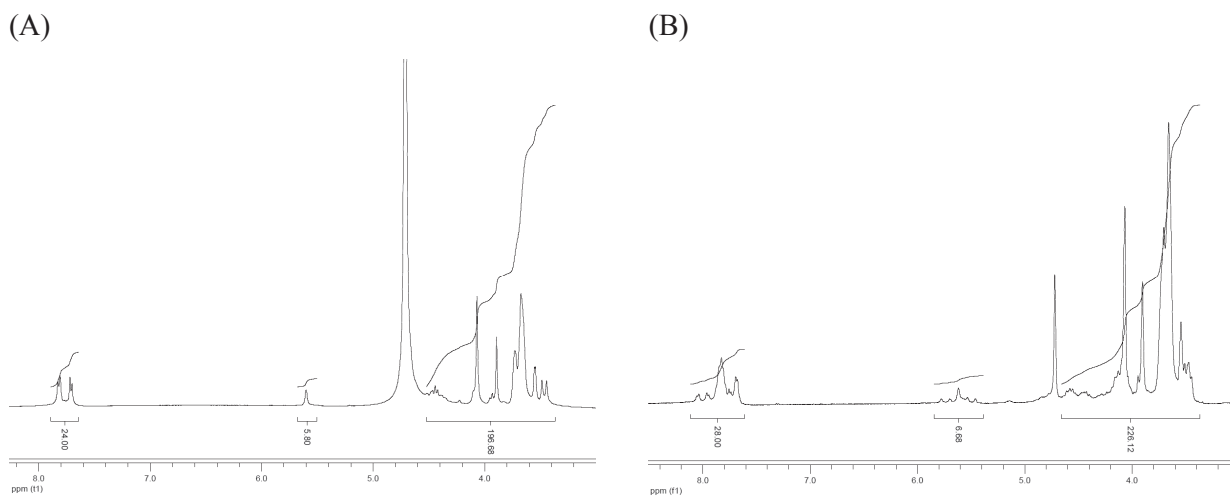


Fig. S2. ¹H NMR spectra of the CD-DO3AP^{NCS} conjugates. (A) L₆- α -CD; (B) L₇- β -CD.

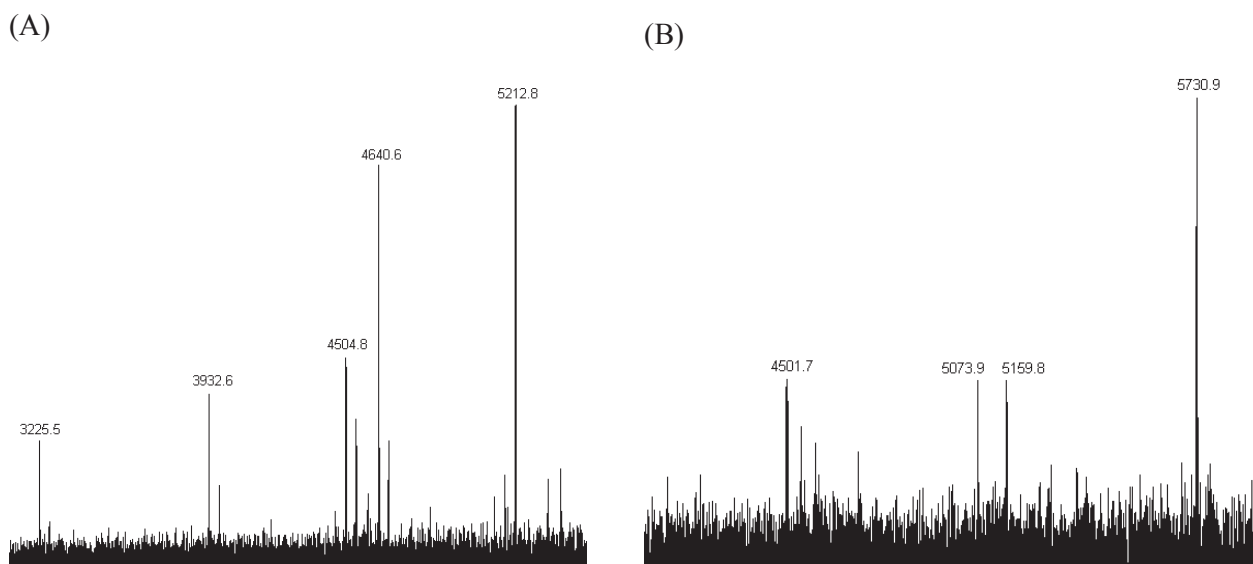


Fig. S3. MALDI-MS spectra of $(LaL)_6-\alpha-CD$ (A) and $(YL)_7-\beta-CD$ (B).

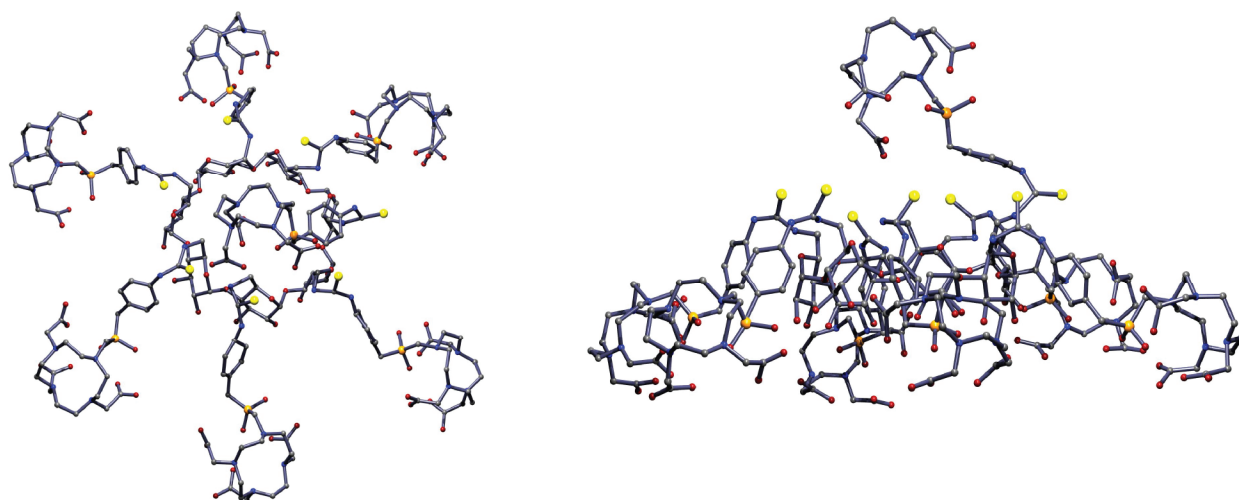


Fig. S4. Suggested solution structure of the $L_7-\beta-CD$ conjugate.

Comparison of steric crowding of conjugates with α and β -cyclodextrins

Let's suggest that cyclodextrin is regular cylindrical molecule. For such a case, its circumference is given by:

$$circ_{CD} = n \cdot d_{SU},$$

where n is a number of sugar units and d_{SU} is mean length of one sugar unit.

The diameter of the cyclodextrin molecule is given by:

$$d_{CD} = circ_{CD} / \pi$$

Let's suggest that conjugate has disc geometry. Thus, after conjugation, the diameter is increased by two mean lengths of complex unit, $d_{complex}$:

$$d_{conjug} = d_{CD} + 2 \cdot d_{complex}$$

The circumference of whole conjugate disc is than:

$$circ_{conjug} = \pi \cdot d_{conjug} = \pi \cdot (d_{CD} + 2 \cdot d_{complex}) = circ_{CD} + 2 \cdot \pi \cdot d_{complex} = n \cdot d_{SU} + 2 \cdot \pi \cdot d_{complex}$$

The part of circumference available for one complex unit is than:

$$circ_{conjug} / n = d_{SU} + 2 \cdot \pi \cdot d_{complex} / n$$

When one is assuming larger $n+1$ cyclooligomer, it gives:

$$circ_{conjug} / (n+1) = d_{SU} + 2 \cdot \pi \cdot d_{complex} / (n+1),$$

i.e. part of circumference available for complex is decreasing with increasing number of sugar units, and therefore, steric crowding in the disc plane increases. E.g., for typical lengths in the cyclodextrin–DOTA-like conjugate case, the distances are $d_{SU} \sim 4.3 \text{ \AA}$ and $d_{complex} \sim 6 \text{ \AA}$, it gives $circ_{conjug} \sim 10.6$ and 9.7 \AA , respectively, for α - and β -cyclodextrin conjugates.

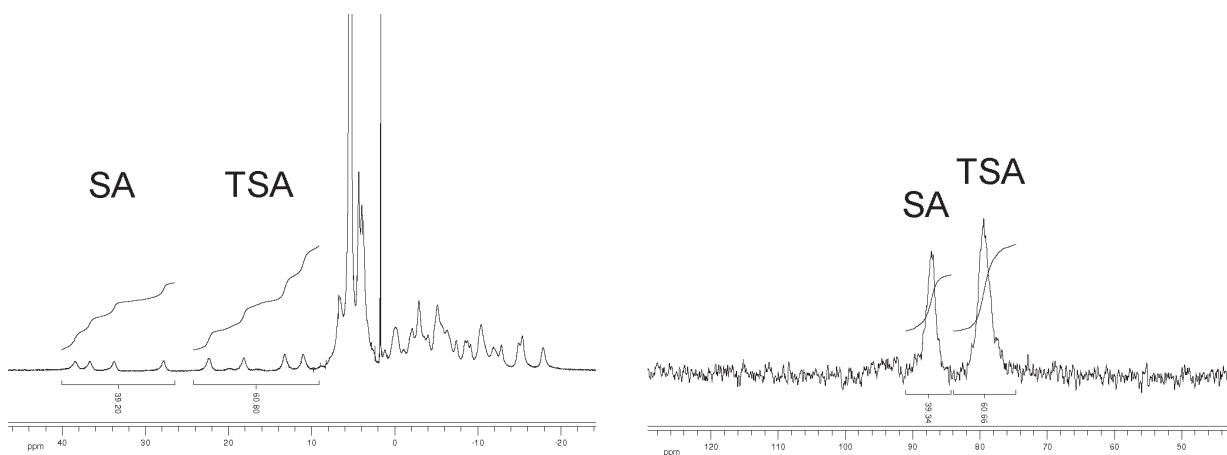


Fig. S5. ^1H and $^{31}\text{P}\{^1\text{H}\}$ NMR spectra of $(\text{EuL})_6\text{-}\alpha\text{-CD}$ (25 °C).

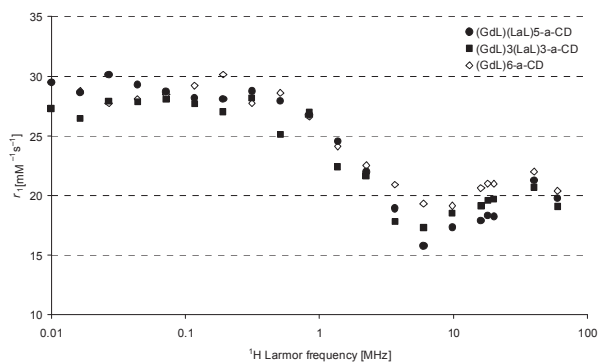


Fig. S6. ^1H NMRD profiles of the $(\text{GdL})_6\text{-}\alpha\text{-CD}$ conjugate and the magnetically diluted species, $(\text{GdL})(\text{LaL})_5\text{-}\alpha\text{-CD}$ and $(\text{GdL})_3(\text{LaL})_3\text{-}\alpha\text{-CD}$, acquired at 25 °C (relaxivity calculated per one Gd^{III} ion).

Table S1. MALDI-MS data for (LaL)₆-α-CD.

Found <i>m/z</i>	Ion ^a	Formula	Calculated <i>m/z</i>
5212.8	[(LaL) ₆ -α-CD+7H] ⁺	C ₁₇₄ H ₂₅₃ La ₆ N ₃₆ O ₇₂ P ₆ S ₆ ⁺	5211.84 (100.0 %)
			5210.84 (86.3 %)
			5212.85 (52.2 %)
4640.6	[(LaL) ₅ -α-CD+La+3H] ⁺	C ₁₅₁ H ₂₁₉ La ₆ N ₃₁ O ₆₄ P ₅ S ₅ ⁺	4639.65 (100.0 %)
			4640.66 (85.2 %)
			4641.66 (58.9 %)
4504.8	[(LaL) ₅ -α-CD+6H] ⁺	C ₁₅₁ H ₂₂₂ La ₅ N ₃₁ O ₆₄ P ₅ S ₅ ⁺	4503.77 (100.0 %)
			4504.77 (99.7 %)
			4502.77 (58.4 %)
3932.6	[(LaL) ₄ -α-CD+La+2H] ⁺	C ₁₂₈ H ₁₈₈ La ₅ N ₂₆ O ₅₆ P ₄ S ₄ ⁺	3932.58 (100.0 %)
			3933.59 (74.6 %)
			3931.58 (66.1 %)
3225.5	[(LaL) ₃ -α-CD+La+H] ⁺	C ₁₀₅ H ₁₅₇ La ₄ N ₂₁ O ₄₈ P ₃ S ₃ ⁺	3225.52 (100.0 %)
			3224.51 (85.2 %)
			3226.52 (66.6 %)

^a As the complexing unit of DO3AP^{ABn} is four-valent acid, the (LaL) complex unit in the formulas above means the fully deprotonated species with one negative charge, *i.e.* (LaL)⁻.

Table S2. MALDI MS data for (YL)₇-β-CD.

Found <i>m/z</i>	Ion ^a	Formula	Calculated <i>m/z</i>
5730.9	[(YL) ₇ -β-CD+8H] ⁺	C ₂₀₃ H ₂₉₅ N ₄₂ O ₈₄ P ₇ S ₇ Y ₇ ⁺	5730.98 (100.0%)
			5729.98 (99.0%)
			5728.98 (82.2%)
5159.8	[(YL) ₆ -β-CD+Y+4H] ⁺	C ₁₈₀ H ₂₆₁ N ₃₇ O ₇₆ P ₆ S ₆ Y ₇ ⁺	5158.79 (100.0%)
			5157.79 (81.3%)
			5159.80 (53.8%)
5073.9	[(YL) ₆ -β-CD+7H] ⁺	C ₁₈₀ H ₂₆₄ N ₃₇ O ₇₆ P ₆ S ₆ Y ₆ ⁺	5072.91 (100.0%)
			5071.91 (88.9%)
			5073.91 (87.0%)
4501.7	[(YL) ₅ -β-CD+Y+3H] ⁺	C ₁₅₇ H ₂₃₀ N ₃₂ O ₆₈ P ₅ S ₅ Y ₆ ⁺	4501.72 (100.0%)
			4500.72 (94.5%)
			4499.72 (52.8%)

^a As the complexing unit of DO3AP^{ABn} is four-valent acid, the (YL) complex unit in the formulas above means the fully deprotonated species with one negative charge, *i.e.* (YL)⁻.

Table S3. Luminescence lifetimes of the (Eu/TbL)₇-β-CD complexes and related compounds (Eu: λ_{ex} 396 nm, λ_{em} 595 and 616 nm; Tb: λ_{ex} 353 nm, λ_{em} 488 and 544 nm).

Compound	τ(H ₂ O) / μs	τ(D ₂ O) / μs	<i>q</i> ^a	Reference
(EuL) ₇ -β-CD	815	2240	0.82/0.64	this work
(TbL) ₇ -β-CD	1750	2730	0.86/0.73	this work
Eu ^{III} -DO3AP ^{ABn}	680	2110	1.05/0.90	this work
Tb ^{III} -DO3AP ^{ABn}	1620	2850	1.12/1.03	this work
Eu ^{III} -DOTA	625	1890	1.12/0.98	ref. ^[1]
Tb ^{III} -DOTA	1515	2560	1.13/1.05	ref. ^[1]

^a Hydration numbers calculated according to Horrocks^[2]/Parker^[1] equations.

Table S4. ^{17}O NMR relaxometric data of $(\text{GdL})_6\text{-}\alpha\text{-CD}$ and $(\text{GdL})_7\text{-}\beta\text{-CD}$ at 54.3 MHz (*i.e.* ^1H 400 MHz, 9.40 T).

T / K	$(\text{GdL})_6\text{-}\alpha\text{-CD}$			$(\text{GdL})_7\text{-}\beta\text{-CD}$		
	$r_1 / \text{s}^{-1} \text{mM}^{-1}$	$r_2 / \text{s}^{-1} \text{mM}^{-1}$	$\omega / \text{rad s}^{-1} \text{mM}^{-1}$	$r_1 / \text{s}^{-1} \text{mM}^{-1}$	$r_2 / \text{s}^{-1} \text{mM}^{-1}$	$\omega / \text{rad s}^{-1} \text{mM}^{-1}$
278.2	2.554	15.37	-11.14	2.717	18.98	-13.12
283.2	2.217	16.38	-13.25	2.617	17.55	-14.31
288.2	2.160	14.92	-12.25	2.278	16.20	-15.18
298.0	1.618	11.72	-13.84	1.756	12.15	-15.37
306.7	1.180	8.786	-12.73	1.375	8.494	-15.37
316.2	0.981	5.821	-12.00	1.095	5.748	-14.11
326.2	0.734	3.965	-11.23	0.826	3.895	-13.29
336.2	0.560	2.436	-10.76	0.637	2.667	-12.67
345.2	0.429	1.632	-10.21	0.488	1.883	-11.61
355.2	0.331	1.127	-9.681	0.367	1.345	-11.16

Table S5. ^1H NMR relaxivities of $(\text{GdL})_6\text{-}\alpha\text{-CD}$ and $(\text{GdL})_7\text{-}\beta\text{-CD}$.

B / MHz	$r_1 / \text{s}^{-1} \text{mM}^{-1}$				
	$(\text{GdL})_6\text{-}\alpha\text{-CD}$		$(\text{GdL})_7\text{-}\beta\text{-CD}$		
	298.2 K	310.2 K	B / MHz	298.2 K	310.2 K
0.0100	29.46	22.38	0.0100	28.50	22.37
0.0164	28.74	23.02	0.0147	28.16	22.60
0.0267	27.90	23.63	0.0214	28.04	22.73
0.0438	28.07	23.54	0.0314	27.93	22.38
0.0716	28.47	23.01	0.0460	28.64	22.58
0.117	29.18	23.02	0.0674	28.67	22.61
0.191	30.14	23.27	0.0985	28.17	22.23
0.313	28.72	22.42	0.144	28.24	22.58
0.512	28.60	22.36	0.211	27.86	22.48
0.837	26.59	22.06	0.310	27.72	22.06
1.37	24.11	20.47	0.453	27.31	21.61
2.24	22.51	17.53	0.663	26.54	21.11
3.66	20.88	15.13	0.971	25.64	20.58
5.98	19.30	14.39	1.42	23.75	19.24
9.78	19.14	13.86	2.08	22.37	17.20
16.0	20.60	13.82	3.05	19.86	15.52
18.0	20.97	13.62	4.46	18.656	14.55
20.0	20.96	13.61	6.53	18.32	13.63
40.0	21.99	15.84	9.56	19.03	14.28
60.0	20.37	15.66	14.0	20.14	14.56
100	14.11	12.10	16.0	21.22	14.93
400	5.90	5.20	20.0	21.65	15.80
			30.0	23.50	17.16
			40.0	23.08	17.03
			60.0	21.34	15.87
			100	16.11	12.84
			400	6.24	5.76

Table S6. ^1H NMR relaxivities of $(\text{GdL})_6\text{-}\alpha\text{-CD}$ and $(\text{GdL})_7\text{-}\beta\text{-CD}$ measured at clinical fields (1.5 and 3.0 T) compared with values predicted by analysis of ^1H NMRD profile (*in italics*). Values of relaxivity are suggested to be loaded by ESD's of approximately $\pm 1 \text{ s}^{-1} \text{mM}^{-1}$ due to range of averaged voxels, and principal error in ensuring temperature stability.

B / T	B / MHz	$r_1 / \text{s}^{-1} \text{mM}^{-1}$			
		$(\text{GdL})_6\text{-}\alpha\text{-CD}$		$(\text{GdL})_7\text{-}\beta\text{-CD}$	
		298.2 K	310.2 K	298.2 K	310.2 K
1.5	63.9	17.8(<i>18.8</i>)	15.3(<i>14.8</i>)	19.8(<i>20.2</i>)	14.2(<i>15.9</i>)
3.0	128.8	13.2(<i>12.6</i>)	12.5(<i>11.3</i>)	12.6(<i>13.7</i>)	12.7(<i>12.3</i>)

// Simultaneous fit of 1H NMRD and 17O T1, T2 and dwr NMR data // Molecular tumbling modelled by Lipari-Szabo approach

IndVars: T,B
DepVars: R1H,lnT1Or,lnT2Or,dwr
// All possible parameters:
// tv0,Ev,delta,dg,n,tm0,Hm,tr0l,tr0IH,tr0g,Erl,ErlH,Erg,RLS,ro,rh,rhos,acc,khi,Cout,nss,tm0ss,Hmss
// It is necessary to choice in maximum 20 of them, otherwise Scientist breaks
Params: tv0,Ev,delta,n,tm0,Hm,tr0l,tr0g,Erl,Erg,RLS,ro,rh,rhos,acc,khi,Cout,nss,tm0ss,Hmss

// Notes

// temperature is in Kelvins
// magnetic field is in Larmor frequencies
// relaxivities and shifts are given per milimolar solution
// "ln" means natural logarithm
// Pm is molar fraction of coordinated water, $Pm = q \cdot c(\text{Gd}) / 55.56$
//
// reduced times T1,2Or are calculated by:
// $T1,2Or = (1/Pm) \cdot (1/T1,2O(\text{Gd-sample})) - 1/T1,2O(\text{blank})$
//
// reduced frequencies (shifts) dwr are calculated by:
// $dwr = B \cdot 10^{-6} \cdot (2 \cdot \pi / c(\text{Gd})) \cdot \{[\text{shift}(\text{O}, \text{Gd-sample}) - \text{shift}(\text{O}, \text{blank})] - [\text{shift}(\text{H}, \text{Gd-sample}) - \text{shift}(\text{H}, \text{blank})]\}$
// where B is in MHz, c(Gd) is in mM and shifts are in ppm
// alternatively
// $dwr = (2 \cdot \pi / c(\text{Gd})) \cdot \{[\text{shift}(\text{O}, \text{Gd-sample}) - \text{shift}(\text{O}, \text{blank})] - (g_0/g_H) \cdot [\text{shift}(\text{H}, \text{Gd-sample}) - \text{shift}(\text{H}, \text{blank})]\}$
// where shifts are in Hz
// be careful, somebody is fitting using frequency wr calculated by
// $wr = B \cdot (2 \cdot \pi / Pm) \cdot \{[\text{shift}(\text{H}, \text{Gd-sample}) - \text{shift}(\text{H}, \text{blank})] - [\text{shift}(\text{O}, \text{Gd-sample}) - \text{shift}(\text{O}, \text{blank})]\}$
// (here, shifts are in ppm scale)
// which can be transferred to dwr by
// $dwr = wr \cdot 10^{-3} / 55.56$

// Parameters and variables used

// T - temperature [K]
// B - used field [MHz for 1H]
// R1H - 1H longitudinal relaxivity [$\text{ms}^{-1} \text{mM}^{-1}$]
// R1O - 17O longitudinal relaxivity [$\text{ms}^{-1} \text{mM}^{-1}$]
// R2O - 17O transversal relaxivity [$\text{ms}^{-1} \text{mM}^{-1}$]
// n - number of water molecules coordinated at Gd
// tm0 - water residence time at 298 K [s]
// tm0ss - water residence time at 298 K for second sphere [s]
// tr0l - local rotation correlation time of Gd-O vector at 298 K [s]
// tr0IH - local rotation correlation time of Gd-H vector at 298 K [s]
// tr0g - global rotation correlation time at 298 K [s]
// trss - rotation correlation time of second sphere [s]
// tv0 - correlation time for instantaneous distortion of the metal coordination polyhedron at 298 K [s]
// dwr - 17O reduced radial frequency difference of bonded and free water [rad s^{-1}]
// delta - Δ^2 , mean squared fluctuation of ZFS
// Erl - rotation free energy (local motion) [kJ mol^{-1}]
// Erg - rotation free energy (global motion) [kJ mol^{-1}]
// Hm - water exchange free energy [kJ mol^{-1}]
// acc - hyperfine Gd-O coupling constant A/\hbar
// ro - Gd-O distance [m]
// rh - Gd-H distance [m]
// rhos - shortest Gd-H distance from outer sphere to Gd [m]
// RLS - degree of spatial restriction of the local motion
// D0 - diffusion coefficient at 298 K
// khi - term with quadrupolar coupling constant and asymmetry parameter = $\chi^* (1 + (\eta^2)/3)^{0.5}$
// Cout - outer sphere contribution to 17O NMR shift
// nss - number of water molecules at second sphere

// rss - Gd-ss distance; sometime simplified that rss=a
// Hmss - water exchange free energy for second sphere contribution

// Physical constants implicitly used

// p - Ludolf's number ($\pi = 3.14159265$)
// univ - universal gas constant ($R = 8.31441 \text{ J mol}^{-1} \text{ K}^{-1}$)
// gh - gyromagnetic ratio of ^1H ($\gamma_{\text{H}} = 2.675\text{E}8 \text{ rad s}^{-1} \text{ T}^{-1}$)
// go - gyromagnetic ratio of ^{17}O ($\gamma_{\text{O}} = -3.626\text{E}7 \text{ rad s}^{-1} \text{ T}^{-1}$)
// gs - electronic gyromagnetic ratio ($\gamma_{\text{S}} = 1.75977\text{E}11 \text{ rad s}^{-1} \text{ T}^{-1}$)
// S - multiplicity of Gd ($S = 3.5$)
// Sz - spin z projection ($S_z = 2*S*(S+1) = 31.5$)
// mB - Bohr magneton ($\mu_{\text{B}} = 9.274\text{E}-24 \text{ J T}^{-1}$)
// m0 - vacuum magnetic susceptibility ($\mu_0 = 4\pi\text{E}-7$)
// h - Planck constant ($h = 6.626071\text{E}-34 \text{ J s}$)
// hbar - reduced Planck constant ($\hbar/(2*\pi) = 1.0546\text{E}-34 \text{ J s rad}^{-1}$)
// NA - Avogadro constant ($NA = 6.023\text{E}23 \text{ mol}^{-1}$)
// k - Boltzmann constant ($k_{\text{B}} = 1.38066\text{E}-23 \text{ J K}^{-1}$)
// g - electron g-factor ($g = 2.0023193043622$)

// C1 = $(1/25)*(4*S*(S+1)-3)$
// C2 = $(1/50)*(4*S*(S+1)-3)$
// C3 = $(1/3)*S*(S+1)$
// C4 = $(1/15)*go^2*g^2*mB^2*(m0/(4*p))^2*S*(S+1)$
// C5 = $(1/5)*(m0/(4*p))^2*(meff^4*mB^4)/(3*k)^2$
// C6 = $2*S*(S+1)*mB/(3*k)*1\text{E}6*2*p/gh$
// C7 = $(2/15)*go^2*g^2*mB^2*(m0/(4*p))^2*S*(S+1)$
// C8 = $((3*p^2)/10)*((2l+3)/(l^2(2l-1)))$; $l=5/2$
// C9 = $(2/15)*((gh^2*g^2*mB^2)*S*(S+1)*(m0/(4*p))^2$
// C10 = $((32*NA*p)/405)*(m0/(4*p))^2*\hbar^2*gs^2*gh^2*S(S+1)$

// Definitions of constants

p=3.14159265
univ=8.31441
gh=2.675E8
go=-3.626E7
gs=1.75977E11
C1=2.4
C2=1.2
C3=5.25
C4=4.7604E-45
C5=3.4274E-59
C6=0.1657
C7=9.5209E-45
C8=0.9475
C9=5.181644E-43
C10=5.796E-19

// Calculation of diffusion coefficient (D)

// Hindman alternative

B1=3.118150E-04
B2=5.062560E+03
B3=1.547920E+02
B4=1.629310E+03
 $D=(1\text{E}-4)/((B1*\text{EXP}(B2/T))+(B3*\text{EXP}(B4/T)))$

// Alternative using activation theory

//D0=25E-10 m² s⁻¹
//ED=22 kJ mol⁻¹
//D0=25E-10
//ED=22E3
 $D=D0*\exp((ED/univ)*((1/298.15)-(1/T)))$

// Definition of molar fraction of coordinated water molecules

$$P_m = n \cdot 10^{-3} / 55.55$$

// Definition of Larmor (angular) frequencies of 1H (wh), 17O (wo) and electron (ws)

$$w_h = 2 \cdot \pi \cdot 10^6 \cdot B$$

$$w_o = 2 \cdot \pi \cdot 10^6 \cdot B \cdot (g_o / g_h)$$

$$w_s = 2 \cdot \pi \cdot 10^6 \cdot B \cdot (g_s / g_h)$$

// Eyring equations

$$t_m = (t_{m0} \cdot 298.15 / T) \cdot \exp(-H_m / \text{univ} \cdot ((1/298.15) - (1/T)))$$

$$t_{mss} = (t_{m0ss} \cdot 298.15 / T) \cdot \exp(-H_{mss} / \text{univ} \cdot ((1/298.15) - (1/T)))$$

$$t_{rl} = t_{rl0} \cdot \exp(-E_{rl} / \text{univ} \cdot ((1/298.15) - (1/T)))$$

$$// t_{rlH} = t_{rl0H} \cdot \exp(-E_{rlH} / \text{univ} \cdot ((1/298.15) - (1/T)))$$

$$t_{rg} = t_{rg0} \cdot \exp(-E_{rg} / \text{univ} \cdot ((1/298.15) - (1/T)))$$

$$t_v = t_{v0} \cdot \exp(-E_v / \text{univ} \cdot ((1/298.15) - (1/T)))$$

// Electronic relaxation times T1e, T2e

// Alternative taking into account only zero field splitting (ZFS)

// McLachlan theory

$$T_{1e} = (C_1 \cdot \delta \cdot t_v \cdot ((1/(1 + w_s^2 \cdot t_v^2)) + (4/(1 + 4 \cdot w_s^2 \cdot t_v^2))))^{-1}$$

$$// T_{2e} = (C_2 \cdot \delta \cdot t_v \cdot (3 + (5/(1 + w_s^2 \cdot t_v^2)) + (2/(1 + 4 \cdot w_s^2 \cdot t_v^2))))^{-1}$$

// Powell alternative

$$T_{2e} = (\delta \cdot t_v \cdot ((5.26/(1 + 0.372 \cdot w_s^2 \cdot t_v^2)) + (7.18/(1 + 1.24 \cdot w_s \cdot t_v))))^{-1}$$

// Alternative including spin rotation (SR) term using local rotational time

$$// T_{1e} = (C_1 \cdot \delta \cdot t_v \cdot ((1/(1 + w_s^2 \cdot t_v^2)) + (4/(1 + 4 \cdot w_s^2 \cdot t_v^2)) + (d_g/(9 \cdot t_{rl}))))^{-1}$$

$$// T_{2e} = (C_2 \cdot \delta \cdot t_v \cdot (3 + (5/(1 + w_s^2 \cdot t_v^2)) + (2/(1 + 4 \cdot w_s^2 \cdot t_v^2)) + (d_g/(9 \cdot t_{rl}))))^{-1}$$

$$// T_{2e} = (\delta \cdot t_v \cdot ((5.26/(1 + (0.372 \cdot w_s^2 \cdot t_v^2))) + (7.18/(1 + 1.24 \cdot w_s \cdot t_v)) + (d_g/(9 \cdot t_{rl}))))^{-1}$$

// Correlation times (t - total, l - local, g - global, e - electronic)

// Dunand suggestion for t_{rlH}/t_{rl} ratio

$$// t_{rlH} = t_{rl} \cdot 0.65$$

// when t_{rlH} and t_{rl} are the same

$$t_{rlH} = t_{rl}$$

$$t_{rt} = (t_{rl}^{-1} + t_{rg}^{-1})^{-1}$$

$$t_{rtH} = (t_{rlH}^{-1} + t_{rg}^{-1})^{-1}$$

$$t_{c1l} = (T_{1e}^{-1} + t_{rt}^{-1} + t_m^{-1})^{-1}$$

$$t_{c2l} = (T_{2e}^{-1} + t_{rt}^{-1} + t_m^{-1})^{-1}$$

$$t_{c1lH} = (T_{1e}^{-1} + t_{rtH}^{-1} + t_m^{-1})^{-1}$$

$$t_{c2lH} = (T_{2e}^{-1} + t_{rtH}^{-1} + t_m^{-1})^{-1}$$

$$t_{c1g} = (T_{1e}^{-1} + t_{rg}^{-1} + t_m^{-1})^{-1}$$

$$t_{c2g} = (T_{2e}^{-1} + t_{rg}^{-1} + t_m^{-1})^{-1}$$

$$t_{e1} = (T_{1e}^{-1} + t_m^{-1})^{-1}$$

$$t_{e2} = (T_{2e}^{-1} + t_m^{-1})^{-1}$$

// Radial frequency difference of bound and free water [rad s⁻¹] (dwm)

$$dwm = (C_6 / T) \cdot \text{acc} \cdot B$$

// Spectral density functions for Lipari-Szabo approach

$$d_{1O} = (RLS \cdot t_{c1g} / (1 + w_o^2 \cdot t_{c1g}^2)) + ((1 - RLS) \cdot t_{c1l} / (1 + w_o^2 \cdot t_{c1l}^2))$$

$$d_{2O} = (RLS \cdot t_{c2g} / (1 + w_s^2 \cdot t_{c2g}^2)) + ((1 - RLS) \cdot t_{c2l} / (1 + w_s^2 \cdot t_{c2l}^2))$$

$$q_{1O} = (RLS \cdot t_{rg} / (1 + w_o^2 \cdot t_{rg}^2)) + ((1 - RLS) \cdot t_{rt} / (1 + w_o^2 \cdot t_{rt}^2))$$

$$q_{2O} = (RLS \cdot t_{rg} / (1 + 4 \cdot w_o^2 \cdot t_{rg}^2)) + ((1 - RLS) \cdot t_{rt} / (1 + 4 \cdot w_o^2 \cdot t_{rt}^2))$$

$$// d_{1H} = (RLS \cdot t_{c1g} / (1 + w_h^2 \cdot t_{c1g}^2)) + ((1 - RLS) \cdot t_{c1l} / (1 + w_h^2 \cdot t_{c1l}^2))$$

$$// d_{2H} = (RLS \cdot t_{c2g} / (1 + w_s^2 \cdot t_{c2g}^2)) + ((1 - RLS) \cdot t_{c2l} / (1 + w_s^2 \cdot t_{c2l}^2))$$

$$d_{1H} = (RLS \cdot t_{c1g} / (1 + w_h^2 \cdot t_{c1g}^2)) + ((1 - RLS) \cdot t_{c1lH} / (1 + w_h^2 \cdot t_{c1lH}^2))$$

$$d_{2H} = (RLS \cdot t_{c2g} / (1 + w_s^2 \cdot t_{c2g}^2)) + ((1 - RLS) \cdot t_{c2lH} / (1 + w_s^2 \cdot t_{c2lH}^2))$$

```
// ***** 17O longitudinal relaxation *****  
//  
// R1 dipolar (pseudocontact) contribution for 17O according to Lipari-Szabo (R1dO)  
R1dO=(C7/(ro^6))*(3*d1O+7*d2O)  
//  
// R1 quadrupolar contribution for 17O according to Lipari-Szabo (R1qO)  
R1qO=C8*khi^2*(0.2*q1O+0.8*q2O)  
//  
// Total T1 relaxation rate/time (R1mO/T1mO)  
R1mO=R1dO+R1qO  
T1mO=(R1mO)^(-1)  
//  
// Overall reduced T1 relaxation of 17O (R1O)  
lnT1Or=ln(1/(T1mO+tm))  
R1O=Pm/(T1mO+tm)  
  
// ***** 17O transversal relaxation *****  
//  
// R2 scalar (contact) contribution for 17O (R2sO)  
R2sO=C3*acc^2*(te1+(te2/(1+ws^2*te2^2)))  
//  
// R2 dipolar (pseudocontact) contribution for 17O according to Lipari-Szabo (R2dO)  
R2dO=(C4/(ro^6))*(7*d1O+13*d2O)  
//  
// R2 dipolar (pseudocontact) Curie contribution for 17O (R2cO)  
//R2cO=(C5*wo^2/(T^2*ro^6))*(4*trg+3*trg/(1+wo^2*trg^2))  
//  
// Total T2 relaxation rate/time (R2mO/T2mO)  
//R2mO=R2sO+R2dO+R2cO  
R2mO=R2sO+R2dO  
//R2mO=R2sO  
T2mO=(R2mO)^(-1)  
//  
// Overall reduced T2 relaxation of 17O (R2O)  
num=(T2mO^(-2))+((T2mO*tm)^(-1)+dwm^2)  
denom=(tm^(-1)+T2mO^(-1))^2+dwm^2  
fract=num/denom  
lnT2Or=ln(fract/tm)  
R2O=Pm*fract/tm  
  
// ***** 17O chemical shift *****  
//  
// Contribution of os (dwos) and total reduced frequency (dwr)  
dwos=Cout*dwm  
dwr=Pm*(dwm/((tm/T2mO+1)^2+(tm*dwm)^2)+dwos)  
  
// ***** 1H longitudinal relaxation *****  
//  
// R1 inner sphere dipolar (pseudocontact) contribution for 1H according to Lipari-Szabo  
// (R1dH, R1His)  
R1dH=(C9/(rh^6))*(3*d1H+7*d2H)  
T1mH=(R1dH)^(-1)  
R1His=Pm/(T1mH+tm)  
//  
// R1 outer sphere contribution for 1H according to Freed (R1Hos);  
// i - 1H nucleus, s - Gd3+ electron  
tau=rhos^2/D
```

```
z2i=(tau/T1e)+([0,1]*wh*tau)
z2s=(tau/T2e)+([0,1]*ws*tau)
os1=Re((1+0.25*(z2i^0.5))/(1+z2i^0.5+(4/9)*z2i+(1/9)*(z2i^1.5)))
os2=Re((1+0.25*(z2s^0.5))/(1+z2s^0.5+(4/9)*z2s+(1/9)*(z2s^1.5)))
R1Hos=(C10/(rhos*D))*(3*os1+7*os2)
//
// R1 second sphere dipolar contribution for 1H (R1Hss)
tc1ss=(T1e^(-1)+trss^(-1))^(-1)
tc2ss=(T2e^(-1)+trss^(-1))^(-1)
R1dHss=(C9/(rhos^6))*((3*tc1ss/(1+wh^2*tc1ss^2))+(7*tc2ss/(1+ws^2*tc2ss^2)))
T1mss=R1dHss^(-1)
Pmss=nss*1E-3/55.55
R1Hss=Pmss/(T1mss+tmss)
//
// Overall R1 proton relaxivity (R1H)
//R1H=R1His+R1Hos+R1Hss
R1H=R1His+R1Hos

// Estimation of parameters
//tv0,Ev,delta,dg,n,tm0,Hm,tr0l,tr0IH,tr0g,Erl,ErlH,Erg,RLS,ro,rh,a,acc,khi,Cout,nss,tm0ss,Hmss
tv0=9.08E-12
Ev=1000
delta=0.0509E20
dg=0.11
n=1
tm0=1.25E-8
Hm=45E3
tr0l=220E-12
//tr0IH=220E-12
tr0g=1950E-12
Erl=22E3
//ErlH=22E3
Erg=22E3
RLS=0.37
ro=2.5E-10
rh=3.1E-10
rhos=3.5E-10
acc=-3.18E6
khi=7.58E6
Cout=0.0
nss=0
tm0ss=1E-9
Hmss=10E3
trss=1E-10
```

References

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- [2] W. D. Horrocks, D. R. Sudnick, *J. Am. Chem. Soc.* **1979**, *101*, 334–340.